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09/733,266	12/08/2000	Richard Kuo	STAN-209	3109

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Pamela J. Sherwood
BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025

EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/733,266	Applicant(s) Kuo et al.
	Examiner Vera Afremova	Art Unit 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 19, 2001* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 13, 15, and 16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 13, 15, and 16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 1, 3-5, 13, 15 and 16 as amended are under examination. Claims 2, 6-12, 14, 17 and 18 were canceled by applicants. [Paper No. 10 filed 9/18/2001].

Response to Arguments

Applicant's arguments filed 9/18/2001 have been fully considered but they are not persuasive for the reason below.

Claim Rejections - 35 U.S.C. § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 15 and 16 as amended remain/is rejected under 35 U.S.C. 102(b) as being anticipated by Grumetto et al. [U] as explained in the prior office action and for the reasons below.

The claims are directed to a method of modulating or activating oocytes wherein the method comprises a step of contacting an oocyte with a donor of nitric oxide (NO donor). Some claims are further drawn to oocyte activation in the absence or presence of sperm.

The cited reference is relied upon as explained in the prior office action and repeated herein.

Grumetto et al. [U] disclose a method of modulating activation of oocytes of the ascidian *Ciona intestnalis* wherein the method comprises a step of contacting an oocyte with a modulator of nitric oxide level or NO donor such as sodium nitroprusside in an *in vitro* system (abstract).

The reference further discloses modulation of NO level or oocyte activation during fertilization (Fig. 4) in the presence of sperm.

The cited reference anticipate the present invention as claimed and as disclosed by application since the cited NO donor or NO precursor such as sodium nitroprusside is regarded as a suitable NO level modulator according applicants' definitions (page 6, lines 25- 27 and page 7, line 11) and the method of the present invention is related to oocytes derived from a wide variety of animal species including invertebrate (page 9, line 11) as the oocytes in the cited method.

Applicants' arguments are directed to the idea that the cited particular NO donor such as sodium nitroprusside (SNP) was not sufficient for oocyte activation as demonstrated in the cited method by the absence of production of first polar body (see response page 4, par. 1). This argument is not found convincing because oocyte activation is regarded (interpreted) by applicants as an increase (or fluctuation) of intracellular Ca^{2+} levels (see instant specification page 5, line 30-31 for definitions and Figures 4-6 for particular results) rather than particular morphological manifestations which might be highly dependent on particular organisms and concentrations of chemicals used. And the cited reference clearly teaches an increase of intracellular Ca^{2+} as the result of addition of NO donor to oocytes (see page 724, col. 2, par. 4, line 2-4). Therefore, the cited method is considered to anticipate the claimed method in the light of those limitations which are presently claimed and disclosed.

Claim 1, 3, 5, 14 and 15 as amended is rejected under 35 U.S.C. 102(b) as being anticipated by Jawerbaum et al. [V] as explained in the prior office action and for the reasons below.

The claim is directed to a method of modulating and/or inhibiting activation of oocytes comprising step of contacting an oocyte with a modulator of nitric oxide NO level such as a donor of NO or an inhibitor of nitric oxide synthase (NOS inhibitor) in an *in vitro* system prior or during fertilization. Some claims are further drawn to oocyte activation in the absence of sperm or prior to sperm addition.

The cited reference is relied upon as explained in the prior office action and repeated herein.

Jawerbaum et al. [V] disclose a method of modulating activation of mammalian oocytes comprising step of contacting *in vitro* cultured and maturated rat oocytes (page 392, par. 3, line 2) with modulators of nitric oxide levels such as NO donors (sodium nitroprusside, for example) and/or inhibitors of nitric oxide synthase (L-NAME, for example) in the absence of sperm.

The cited method is considered to anticipate the claimed method because both methods comprise identical step of contacting identical oocytes with identical modulators. The cited oocytes have been recovered from mammalian follicles and matured by *in vitro* hormone treatment as the applicants' oocytes as intended (see specification page 5, line 24-26).

Applicants' argument is drawn to the idea that the cited reference is not anticipate the claimed method because it demonstrates only modulation of prostaglandin synthesis by applying

NO donors or NOS inhibitors but it is silent with regard to activation of oocytes or it does not teach a link between prostaglandin synthesis and modulation/activation of oocyte. This is not found convincing since the claimed method is one active step method of contacting identical oocyte with identical compound such as NO donor or NOS inhibitor. Thus, the final result is reasonably expected to be inherently identical. Moreover, the cited reference teaches that it is known that NOS inhibitors diminish fertilization rate in vitro (page 393, col. 1, par. 1 at section "Discussion", par. 1). And, further, the cited reference also teaches that NO level, which is modulated by NO donors and/or NOS inhibitors, mediates hormone-induced production of prostaglandin and, thus, NO donors or NOS inhibitors are directly involved in mammalian oocyte maturation, ovulation and fertilization processes.

Claim Rejections - 35 U.S.C. § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 13, 15 and 16 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over Grumetto et al. [U] taken with Jawerbaum et al. [V] and US 6,077, 710 [IDS-AB] as explained in the prior office action and for the reasons below.

The claim is directed to a method of modulating activation of oocytes comprising step of contacting an oocyte with a modulator of nitric oxide level such as a donor of NO or an inhibitor of nitric oxide synthase (NOS inhibitor) in an *in vitro* system. Some claims are further drawn to

oocyte activation/modulation in the absence of sperm or prior to sperm addition. Some claims are further drawn to the use of oocytes including mammalian or human oocytes.

The cited references by Grumetto et al. [U] and Jawerbaum et al. [V] are relied upon as explained above for the disclosure of methods of modulating activation of oocytes by contacting oocytes with modulators of NO levels such as NO donors or NOS inhibitors.

And, further, the cited reference by Grumetto et al. [U] also teaches an induction of fertilization current or Ca^{2+} currents by modulation of NO level (abstract). But it is lacking the teaching related to activation of mammalian oocytes.

The secondary reference US 6,077, 710 [IDS-AB] teaches that activation of mammalian oocytes is a function of calcium (Ca^{2+}) (col. 2, line 42) and that parthenogenic activation of oocytes prior to nuclear transfer and related to repetitive transient elevations in intracellular Ca^{2+} in mammalian oocytes (col. 2, lines 47-50 and col. 3, lines 3-10) including various mammalian oocytes such as rabbit, bovine and/or mouse oocytes.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the present invention as claimed with a reasonable expectation of success in activating oocytes with NO level modulators because the prior art teaches that activation of oocytes and/or fertilization channels are modulated by NO levels [U] and activation of oocytes is related to Ca^{2+} fluctuations in oocytes including mammalian oocytes belonging to various mammalian species [IDS-AB]. The method of the present invention is related to activation of oocytes derived from a wide variety of animal species including

invertebrate species, mammalians and etc. (specification page 9, line 11) as demonstrated by the cited prior art [U, V, IDS-AB]. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Applicants' main argument is directed to the idea that the cited references combined do not provide a clear connection between modulating NO levels and mammalian oocyte activation and/or fluctuations of Ca^{2+} levels. This is not found particularly convincing since the references by Grumetto et al. [U] teaches an induction of fertilization current or fluctuations of Ca^{2+} levels by modulation of NO level (see abstract, for example). And the cited US 6,077, 710 [IDS-AB] teaches that activation of oocytes or reentry into mitotic cycle of mammalian oocytes is directly related to cellular activity which is a function of Ca^{2+} levels (col. 2, lines 32-42). 42) and that activation of oocytes of various mammalian species is characterized by fluctuations of intracellular Ca^{2+} levels (col. 3, lines 3-30).

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SANDRA E. SAUCIER
PRIMARY EXAMINER

Vera Afremova,

Art Unit 1651

November 20, 2001.